REMARKS

It is well known in the art that decreased susceptibility to atherosclerosis and related cardiovascular disease is generally inversely correlated with increased absolute levels of circulating high density lipoprotein (HDL) and also increased levels of HDL relative to circulating levels of very low density lipoprotein (VLDL) and low density lipoprotein (LDL). Cholesteryl ester transfer protein (CETP) mediates the transfer of cholesteryl ester from HDL to triglyceride-rich lipoproteins such as VLDL and LDL, (see, e.g., p. 1, lines 19-22, of Applicants' specification). High CETP activity has been correlated with decreased levels of HDL-associated cholesterol and with increased levels of LDL-associated cholesterol and VLDL-associated cholesterol, which increased levels in turn are correlated with conditions that are associated with an increased risk of cardiovascular disease (p. 1, lines 25-34, of Applicants' specification). Conversely, low CETP activity has been associated with increased levels of HDL circulating in the bloodstream, a condition which reduces the risk of developing heart disease.

The present invention relates to the concept of modulating or inhibiting endogenous CETP activity in a mammal in order to control the relative levels of lipoproteins, in particular to increase the level of HDL in an individual by generating auto-antibodies in a vaccinated subject against that subject's endogenous CETP (see, p. 3, lines 8-14, of Applicants' specification). Applicants' novel approach, however, is not to directly regulate CETP activity by injection of inhibitory substances. Rather, Applicants' invention provides methods and compositions for actively immunizing a subject against their own endogenous CETP in order to raise HDL-cholesterol levels. In other words, Applicants propose to induce antibody recognition, by a subject's own immune system, of the subject's own, endogenous (or "self") CETP. Such immune recognition of self results in modulation and inhibition of CETP activity with beneficial effects. Specifically, as discussed more fully below, Applicants made the surprising discovery of a method whereby administration of a vaccine composition comprising a whole CETP protein conjugated to a carrier peptide to a mammalian subject results in the generation of antibodies (autoantibodies) that recognize the mammal's (own) endogenous CETP, effectively inhibiting CETP activity, i.e., preventing the transfer of cholestryl esters from HDL to LDL thereby increasing the levels of HDL-cholesterol ("good cholesterol") circulating in the bloodstream, which in turn results in a decrease in the amount of total cholesterol circulating in the bloodstream, a decrease in the amount of LDL ("bad") cholesterol circulating in the bloodstream, and a reduction in the development of atherosclerotic plaques in the arteries of rabbits administered this vaccine composition as compared with control rabbits administered an irrelevant human chorionic gonadotropin (HCG) composition.

In particular, the claimed methods of the invention comprise administering to a human or animal a vaccine composition comprising a whole CETP protein conjugated to a carrier peptide such as keyhole limpet hemocyanin (KLH) (see, p. 4, line 28 to p. 5, line 9.) The methods of the invention induce production of antibodies (i.e., autoantibodies) in an individual that specifically target and inhibit the individual's endogenous CETP to obtain the beneficial result of lipoprotein profiles (such as an increase in HDL and a decrease in total cholesterol and LDL) that are correlated with a decreased risk of atherosclerosis, i.e., to decrease or prevent development of atherosclerotic lesions.

To support the teachings of the present specification and claims, Applicants submit herewith the declaration pursuant to 37 C.F.R. §1.132 of Lawrence J. Thomas, Ph.D., the Associate Director, Pharmacology/Toxicology of Avant Immunotherapeutics, Inc. (the Assignee of the present application). Dr. Thomas' declaration presents the protocol and results of New Zealand White rabbits vaccinated with a composition comprising a full-length human CETP conjugated to a tetanus toxoid carrier peptide. As seen in Dr. Thomas' results, vaccination of the rabbits with this composition resulted in the generation of rabbit anti-CETP antibodies that recognized the rabbit's endogenous CETP (see, Exhibit A, Tab A). Generation of these autoantibodies significantly inhibited the level of total cholesterol circulating in the bloodstream (see, Exhibit B, Tab B), cholesterol deposits in the eye (see, Exhibit D, Tab D), and the level of LDL-cholesterol circulating in the bloodstream (see, Exhibit C, Tab C). This treatment also led to a reduction in the development of atherosclerotic lesions in the arteries of rabbits vaccinated with the composition, as compared to control rabbits vaccinated with an irrelevant antigen, human chorionic gonadotropin (HCG) (see, Exhibit E, Tab E).

Therefore, Dr. Thomas' data illustrates the benefits of the claimed methods of the present invention by demonstrating that a vaccine composition comprised of a full-length human CETP conjugated to a carrier and administered to a mammal, results in the generation of auto-antibodies against the endogenous CETP of the subject, which antibodies are capable of altering the lipoprotein profile of the mammal by inhibiting CETP activity to increase the level of HDL-cholesterol circulating in the bloodstream and decreasing the level of LDL-cholesterol circulating in the bloodstream to effectively prevent or reduce development of atherosclerotic plaques.

Applicants have amended the claims to more particularly recite the invention disclosed in the present application. Specifically, the subject matter of Claims 1 and 6 have been combined and Claim 1 now specifies that the immunogenic composition recited therein is comprised of a full-length CETP protein conjugated to a carrier, said composition being capable of raising antibodies against the vaccinated subject's endogenous CETP. Support for the amendment to Claim 1 may be found throughout the specification, e.g., p. 3, lines 8-28, and original Claim 6.

Claims 2, 5, and 6 have been canceled herein.

Claims 7, 8, and 10-13 have been amended to depend from pending (non-canceled) claims.

No new matter has been added by these amendments. Entry of the amendments is respectfully requested.

Objection under 37 C.F.R. §1.75(c)

The Examiner has objected to Claim 8 as being in improper form in that it is a multiple dependent claim that does not refer back in the alternative. In response, Applicants have amended Claim 8 to recite "The method of Claim 1 or 7, . . ."

Reference to Claims 5 and 6 in Claim 8 have been deleted as Claim 5 has been canceled in its entirety and Claim 6 has been canceled and its subject matter incorporated into Claim 1. Entry of the amendment to Claim 8 is respectfully requested.

Rejection Under 35 U.S.C. § 102(b)

The Examiner has rejected Claims 1, 2, 5, 9, 11, and 13 as anticipated by Swenson et al., *J. Biol. Chem.*, 264(24): 14318-14326 (1989). According to the Examiner, with respect to Swenson et al.,

> "Swenson et al. disclose of immunizing a mammal with full length CETP, and obtaining an antibody which was elicited against the CTEP [sic] immunogenic composition . . . Furthermore, since Swenson et al. administered human CTEP [sic] as the immunogenic composition it is deemed to inherently comprise the sequence recited as SEQ ID NO: 1 of the instantly claimed invention, since it too is a human CTEP [sic] sequence." (See, Office Action, page 3.)

Swenson et al. describe the isolation of a murine monoclonal antibody, designated TP2, that binds to an epitope contained within the carboxy-terminal 26 amino acids of human CETP. Comparative binding assays performed with TP2 indicated that complexing of TP2 with CETP interfered with the neutral lipid binding activity of CETP and enhanced binding of CETP to lipoproteins. There is no mention in Swenson et al. of the concept of active immunization of an individual to continuously control CETP activity via an endogenous immune response in order to alter the lipoprotein profile of the treated subject.

While Swenson et al. may show the use of xenogeneic human CETP or CETP fragments to immunize mice and raise murine anti-human CETP antibodies for *in vitro* use (e.g., immunoblots, assays, purification protocols), there is no teaching of raising anti-mouse CETP antibodies in mice or anti-rabbit CETP antibodies in rabbits. In other words, the Examiner's observation that Swenson et al. "obtain[ed] an antibody which was elicited against the CETP immunogenic composition" is not an observation of antibodies recognizing endogenous CETP (as required in the present claims), i.e., is not an immunization against a self CETP.

Also, claims as amended specify a conjugate of CETP and a carrier, which is not shown by Swenson et al.

Accordingly, the Swenson et al. reference is insufficient to anticipate any of the pending claims under 35 U.S.C. §102(b). Reconsideration and allowance of the claims are respectfully requested.

Rejection under 35 U.S.C. §103

The Examiner has rejected Claims 1, 2, 5-7, and 9-13 under 35 U.S.C. §103 as being unpatentable over Swenson et al., *supra.* in view of Nagashima et al., Cloning and mRNA tissue distribution of rabbit cholesteryl ester transfer protein, *Journal of Lipid Research*, 29: 1643-1649 (1988) ("Nagashima et al.") and Maciak et al., U.S. Pat. No. 5,264,341, Selective Cloning For High Monoclonal Antibody Secreting Hybridomas ("Maciak et al.").

According to the Examiner,

> "Nagashima et al. . . . teach of the sequence of rabbit CETP and its overall sequence homology of 81% compared to human CTEP [sic], with two thirds of the amino acid substitutions being conservative. Nagashima et al. further teach of extensive structural similarity between rabbit and human CETP." (See, Office Action, page 4.)

and

> "Maciak et al. . . . teach that at the time of the invention it was well known that carriers, such as KLH, could be conjugated to a non-immunogenic molecule to render the molecule immunogenic." (See, Office Action, page 4.)

However, what is missing from the Examiner's reference combination is any hint or suggestion from the prior art that endogenous CETP is a suitable, desirable, or plausible auto-immunization target. Applicants assert that none of the cited references, either alone or in combination, recognize or address the problem of controlling endogenous CETP activity in an individual via production of autoantibodies against the endogenous CETP. Nor is there any conception from the citations of producing an anti-atherogenic condition via inducing an immune response to control endogenous CETP activity to favorably affect the lipoprotein profile of the vaccinated subject. And there is certainly no suggestion from the references that the immunogenic compositions and methods of the present invention would be effective to overcome the innate tolerance to self CETP and cause an immune response which, in turn, would recognize and control the activity of endogenous CETP, which immune response, in turn, would be sufficiently great to alter cholesterol levels in circulation (i.e., increase HDL-cholesterol, decrease LDL-cholesterol and total cholesterol), which alteration, in turn, would be sufficient to inhibit development of atherosclerotic plaques in vaccinated subjects.

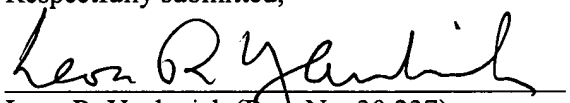
The disclosure of the Swenson et al. reference is as described above and the Examiner has not provided any reasons why one skilled in the art would either combine these references or interpret them as teaching or disclosing Applicants' claimed invention, i.e., vaccinating an individual with a CETP protein conjugated to a carrier peptide in order to elicit auto-antibodies against that individual's endogenous CETP.

The Nagashima et al. reference simply discloses the amino acid sequence of rabbit CETP but makes no mention of the use of the protein in an immunogenic composition to raise autoantibodies against the rabbit's endogenous CETP, i.e., to break the rabbit's natural tolerance to a self protein. Maciak et al. simply discloses a well known scientific fact (that Applicants disclose in the specification), i.e., that a hapten is more likely to generate an immune response if conjugated to an immunogen. (See, p. 4, line 28, to p. 5, line 9.)

Therefore, the combination of Swenson et al. (immunizing mice with a human protein to raise murine anti-human antibodies), Nagashima et al. (amino acid sequence of rabbit CETP), and Maciak et al. (a hapten conjugated to an immunogen improves immunogenicity) does not disclose or suggest to one skilled in the art, vaccination of a subject with a full-length CETP protein linked to a carrier to generate an auto-immune response, i.e., to generate auto-antibodies against the vaccinated subject's endogenous CETP, as a method for treating or preventing cardiovascular disease.

In view of all of the above comments, Applicants submit that the claims of the application are in condition for allowance. Accordingly, Applicants respectfully request that the Examiner enter the amendments to the claims and pass this application to issue.

Respectfully submitted,



Leon R. Yankwich (Reg. No. 30,237)
David G. O'Brien (Reg. No. 46,125)
Attorneys for Applicants
YANKWICH & ASSOCIATES, P.C.
201 Broadway
Cambridge, Massachusetts 02139
telephone: (617) 374-3700
telecopier: (617) 374-0055

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